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1: Br J Cancer 2003 Apr 22;88(8):1223-8

Related Articles, Li

BJC British Journal of Cancer

Overexpression of leucocyte common antigen (LAR) P-subunit in thyroid carcinomas.

Konishi N, Tsujikawa K, Yamamoto H, Ishida E, Nakamura M, Shimada K, Yane K, Yamashita H, Noguchi S.

Protein tyrosine phosphatase (PTPase) dephosphorylation and protein tyrosine kinase (PTKs) phosphorylation of key signal transduction proteins may be regulated by extracellular signals, making PTPases important in the regulation of cell proliferation. Leucocyte common antigen (LAR), a receptor-like PTPase, consists of E-subunit, containing the cell adhesion molecule-lik receptor region, and P-subunit specific for a short segment of tl extracellular region, the transmembrane peptide, and two cytoplasmic PTPase domains. We produced a monoclonal antibody against the LAR P-subunit for immunohistochemical screening of LAR expression in normal and tumourous tissues. Gliomas and gastric, colorectal, lung, breast and prostate cancer showed weak and relatively infrequent expression. Intense and diffuse expression, however, was detected in 95% (227 out of 239) of thyroid carcinomas, but only 12% (22 out of 128) of adenomas and no cases of benign thyroid disease were immunopositive. In contrast to broad staining in carcinomas, LAI expression in thyroid adenomas was often found in small focal o locally invasive areas. Western blot analysis similarly detected LAR P-subunit protein in thyroid carcinomas, but not in normal tissues. We believe this to be the first demonstration of LAR overexpression in thyroid carcinoma and may help to elucidate the role of PTPases in the development of malignancy.British Journal of Cancer (2003) 88, 1223-1228. doi:10.1038/sj.bjc.6600876www.bjcancer.com

PMID: 12698188 [PubMed - in process]

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☑	USPT	L3 and (L2 or L1)	YES	ADJ	ASSIGNEE	L4
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***179590**

Links

PROTEIN-TYROSINE PHOSPHATASE, RECEPTOR-TYPE, F; PTPRF

Alternative titles; symbols

RECEPTOR-LINKED PROTEIN-TYROSINE PHOSPHATASE LAR
LEUKOCYTE ANTIGEN-RELATED TYROSINE PHOSPHATASE; LAR

Gene map locus 1p32

TEXT

The LAR gene (symbolized PTPRF) encodes a membrane protein that has a cytoplasmic domain with homology to protein-tyrosine phosphatase 1B (176885) and an extracellular domain homologous to the neural cellular adhesion molecule NCAM (116930).

The human LAR molecule closely resembles cell adhesion molecules, which suggests that it may be involved in the regulation of phosphotyrosine levels through cell-cell or cell-matrix interactions. As a first step toward site-directed mutagenesis studies of LAR function, Schaapveld et al. (1995) characterized the mouse Ptprf gene. They found that its cytoplasmic region is encoded by 11 exons that span only 4.5 kb of genomic DNA. Compared to the known exon-intron structures of other mammalian receptor-like protein tyrosine phosphatase genes such as Ptpra (encoding LRP; 176884) and Ptprc (coding for Ly-5; 151460), the portion of the Ptprf gene encoding the cytoplasmic region of murine LAR contained not only smaller, but also fewer introns.

O'Grady et al. (1994) demonstrated that the human LAR gene is composed of 33 exons spanning over 85 kb. Exon 2 encodes the signal sequence and the first 4 amino acids in the mature LAR protein. The 3 immunoglobulin-like domains are encoded by exons 3 to 7, and the 8 fibronectin type III (FN-III) domains by exons 8 to 17. Exons 18 to 22 encode the juxtamembrane and transmembrane domains, and exons 23 to 33 encode the 2 conserved tyrosine phosphatase domains and the entire 3-prime untranslated region. Alternative splicing of LAR mRNA was revealed by RT-PCR analysis.

Ahmad and Goldstein (1997) reported that LAR is synthesized as an approximately

200-kD protein that is proteolytically processed into 2 noncovalently associated subunits: a 150-kD extracellular (E) subunit that contains the cell adhesion molecule domains, and an 85-kD phosphatase (P) subunit that contains extracellular, transmembrane, and cytoplasmic domains. Ahmad and Goldstein (1997) carried out several studies to elucidate the relationship between LAR and the insulin signaling pathway. They demonstrated that anti-LAR antibodies inhibit the activity of overexpressed human insulin receptor (147670) in Chinese hamster ovary cells. Immunoprecipitation of LAR from cell lysates and immunoblotting with antibody to the insulin receptor (or vice versa) showed a physical association between LAR and the insulin receptor. In insulin-stimulated rat liver cells, LAR was temporally internalized into a similar endosomal compartment as the insulin receptor. Ahmad and Goldstein (1997) concluded that LAR acts as a protein-tyrosine phosphatase that negatively regulates the insulin signaling pathway.

Nam et al. (1999) determined the crystal structure of the tandem D1 and D2 domains of the human LAR.

By in situ hybridization, Disteche et al. (1989) mapped the LAR gene to 1p34-p32. The related leukocyte common antigen (LCA, also known as CD45; 151460) also maps to chromosome 1. By in situ hybridization, Jirik et al. (1992) mapped LAR, a putative tumor suppressor gene, to 1p32, a region frequently deleted in human neuroblastoma and pheochromocytoma. By fluorescence in situ hybridization, Schaapveld et al. (1995) mapped the Ptprf gene to mouse chromosome 4. Harder et al. (1995) found that coamplification of the PTPRF gene and the MYCL1 gene (164850) in a small cell lung cancer line supported close linkage of the 2 genes.

Most receptor-like transmembrane protein-tyrosine phosphatases (PTPases) such as CD45 and the PTPRF molecule have 2 tandemly repeated PTPase domains in the cytoplasmic segment. Tsujikawa et al. (2001) examined the function of each PTPase domain of PTPRF in vivo using a potential physiologic substrate, insulin receptor, and PTPRF mutant proteins. PTPRF associated with and preferentially dephosphorylated the insulin receptor that was tyrosine phosphorylated by insulin stimulation. Its association was mediated by PTPase domain 2, because the cys1813-to-ser mutation in domain 2 resulted in weakening of the association. The cys1522-to-ser mutant protein, which is defective in the PTPRF PTPase domain 1 catalytic site, was tightly associated with tyrosine-phosphorylated insulin receptor, but failed to dephosphorylate it, indicating that PTPRF PTPase domain 1 is critical for dephosphorylation of tyrosine-phosphorylated insulin receptor. The authors concluded that each domain of PTPRF plays distinct functional roles through phosphorylation and dephosphorylation in vivo.

Schaapveld et al. (1997) used gene targeting in mouse embryonic stem cells to generate mice lacking sequences encoding both LAR phosphatase domains. Homozygous mutant mice develop and grow normally. However, mammary glands of homozygous LAR-deficient females were incapable of delivering milk due to an impaired terminal differentiation of alveoli at late pregnancy. The authors concluded that LAR-mediated signaling may play an important role in mammary gland development and function.

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CONTRIBUTORS

John A. Phillips, III - updated : 7/31/2001
Stylianos E. Antonarakis - updated : 7/2/1999
Rebekah S. Rasooly - updated : 10/7/1998
Rebekah S. Rasooly - updated : 4/9/1998

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7/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09536218 BIOSIS NO.: 199497544588

Mutational analysis of proprotein processing, subunit association, and shedding of the LAR transmembrane protein tyrosine phosphatase.

AUTHOR: Serra-Pages Carles(a); Saito Haruo; Streuli Michel
AUTHOR ADDRESS: (a)Div. Tumor Immunol., Dana Farber Cancer Inst., Boston, MA 02115**USA

JOURNAL: Journal of Biological Chemistry 269 (38):p23632-23641 1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **LAR** transmembrane protein tyrosine phosphatase (PTPase) is expressed on the cell surface as a complex of two noncovalently associated subunits derived from a proprotein. The 150-kDa E-subunit contains most of the extracellular region, including the immunoglobulin-like and fibronectin type-III-like domains, whereas the 85-kDa **P - subunit** contains a short ectodomain, the transmembrane peptide, and the two intracellular PTPase domains. The **LAR** extracellular region is released from the cell surface, suggesting that shedding may be a mechanism to regulate IAR PTPase function. Functional regions necessary for IAR proprotein processing, subunit association, and shedding were determined by analyzing the effect of amino acid substitutions of residues surrounding the cleavage site and scanning the **P - subunit** ectodomain. Three amino acid residues were identified, two within a penta-arginine sequence and one C-terminal to the cleavage site, that are essential for efficient **LAR** proprotein cleavage. Several noncontiguous amino acid residues were also identified that play an essential role in **LAR** subunit association. **LAR** shedding is shown to be a consequence of proteolytic cleavage at a second site within the **P - subunit** ectodomain near the transmembrane peptide.

Set	Items	Description
S1	2703	LAR
S2	0	TYROSINE PHOPHATASE
S3	560	TYROSINE PHOSPHATASE
S4	72	P(W)SUBUNIT
S5	0	S1 AND S3 AND S4
S6	5	S1 AND S4
S7	3	RD (unique items)

1/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09096593 BIOSIS NO.: 199497104963
Characterization of AE-6 monoclonal antibody recognizing VHCSAGV **sequence in CD45 PTPase domain.**
AUTHOR: Takeuchi Tsutomu; Sekine Hiromi; Koide Jun; Abe Tohru
AUTHOR ADDRESS: Saitama Med. Sch., Saitama**Japan
JOURNAL: Tissue Antigens 42 (4):p441 1993
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ISSN: 0001-2815
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LANGUAGE: English
REGISTRY NUMBERS: 79747-53-8: PROTEIN TYROSINE PHOSPHATASE
DESCRIPTORS:
MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology)
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): animals; chordates; humans; mammals; primates; vertebrates
CHEMICALS & BIOCHEMICALS: PROTEIN TYROSINE PHOSPHATASE
MISCELLANEOUS TERMS: FIBRONECTIN DOMAIN; MEETING ABSTRACT; PROTEIN TYROSINE PHOSPHATASE; SIGNAL TRANSDUCTION; TISSUE ANTIGEN
CONCEPT CODES:
02508 Cytology and Cytochemistry-Human
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10506 Biophysics-Molecular Properties and Macromolecules
10508 Biophysics-Membrane Phenomena
10806 Enzymes-Chemical and Physical
10808 Enzymes-Physiological Studies
15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
10068 Biochemical Studies-Carbohydrates
BIOSYSTEMATIC CODES:
86215 Hominidae